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Research Article

Preoperative Pregabalin Prolongs Spinal Anesthesia in Total Knee Arthroplasty - A Retrospective Analysis

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Abstract

Background: Pregabalin is a gamma aminobutyric acid analogous, which is commonly used for epilepsy, neuropathic pain and anxiety disorder. Moreover, it is becoming more commonly used for acute postoperative pain. The recent studies showed that preoperative use of pregabalin increases the duration of spinal anesthesia. Thus, we conducted a retrospective analysis to investigate whether preoperative pregabalin affect duration of spinal anesthesia in total knee arthroplasty.

Methods: 76 patients who underwent unilateral or bilateral total knee arthroplasty were included in the study. The patients were divided in two groups based on their preoperative use of pregabalin; Pregabalin Group (patients who took pregabalin (at least 150 mg/day) at home for osteoarthritis vs. Control Group (patients were not on any gabapentinoids (pregabalin or gabapentin)). Two cohorts were matched by age and gender. All patients received spinal anesthesia with 10 mg of isobaric 0.5% bupivacaine.

Results: There was no statistical difference in the time of sensory block reached to sixth thoracic dermatome in two groups. The duration of two segment regression from peak sensory block level in pregabalin group was significantly longer than control group (70 ± 22.4 min) vs. 40 ± 12.4 min, P = 0.0001). The entire duration of motor block was significantly longer in pregabalin group (200 ± 36.7min vs. 180 ± 26.5 min, P = 0.0001).

Conclusion: The duration of spinal anesthesia was longer in patients who took pregabalin as a home medication than patients who were not on this medication.

Keywords: *Pregabalin; Spinal Block; Total Knee Arthroplasty*

Introduction

Knee Osteoarthritis is a common medical disorder. It is considerably painful and disabling especially in the late stage and many may require surgery to reduce pain and increase functionality. Osteoarthritis pain is considered to be inflammatory origin as well as it has neuropathic component of pain. Non-steroidal inflammatory drugs are common pain medications for osteoarthritis. Recently, pregabalin has gained popularity to treat chronic osteoarthritis knee pain. Pregabalin is a lipophilic analogue of gamma-aminobutyric acid and binds the alpha-2-delta-1 subunit of voltage-gated calcium channels of "over-excited" pre-synaptic neurons, thereby changes the conformation of the channel and reduces the release of excitatory neurotransmitters such as glutamate, calcitonin and substance P [1]. It has been used to treat epilepsy, neuropathic pain, and anxiety disorder [1,2]. In addition, it is becoming more commonly used as a part of multimodal analgesia during perioperative period. A meta-analysis shows that perioperative use of pregabalin reduces opioid consumption and opioid related adverse effects [3]. In addition to the studies done in patients who received general anesthesia, a few studies have shown that preoperative pregabalin helps to improve postoperative analgesia or reduce opioid use in patients who received regional anesthesia such as spinal or epidural anesthesia [4-6]. One study showed that preoperative use of pregabalin prolongs the duration of spinal block in urogenital surgery [5]. Accordingly, we conducted retrospective study investigating duration of spinal anesthesia in patients who took pregabalin as a home medication in elective total knee arthroplasty (TKA). Our hypothesis was that pregabalin increases the duration of spinal anesthesia in patients who undergo elective TKA.

Methods

This retrospective study was approved by the local Institutional Review Board (02/14/2013 2013/341). Patients who underwent elective TKA between January 2012 to January 2013 were included in the study. Inclusion criteria were: a) unilateral or bilateral TKA under spinal anesthesia, b) 18 years old or older and c) American Society of Anesthesiologists (ASA) physical status I - III. Patients who received other than spinal anesthesia (i.e. general, epidural, sedation) were excluded.

Patients' medical records were reviewed and divided into two groups based on their preoperative pregabalin usage; Pregabalin Group: patients who took pregabalin (at least 150 mg/day) at home for osteoarthritis. Control Group: patients who were not on any gabapentinoids (pregabalin or gabapentin) preoperatively. Two cohorts were matched by age and gender. In Pregabalin Group, patients were given 150 mg of pregabalin 2 hours before surgery. Premedication such as midazolam was not used prior to surgery. Typically, spinal anesthesia was administered in L3-4 or L4-5 interspace using a 25-gauge spinal needle in sitting position. After confirmation of cerebral spinal fluid, 10 mg of isobaric 0.5% bupivacaine was injected. After the injection, patient was placed in supine position for surgery. Sensory block was monitored using the Pinprick test. Time for sensory block reached to the sixth thoracic (T6) dermatome and two-segment regression in sensory block were included in the analysis. Motor block was assessed using the Modified Bromage Score (0 = No motor block, 1 = Inability to raise extended leg; able to move knees and feet, 2 = Inability to raise extended leg and move knee; able to move feet, 3 = Complete motor block of limb). The duration of motor block was defined as from the time of complete block (score 3) to the time of resolution of block (score 0). Standard monitors including blood pressure, pulse oximetry and electrocardiography (ECG) were utilized during surgery.

Statistical analysis was performed with the SPSS for Windows Statistical Software Package, SPSS Inc, Chicago, IL, USA). Fisher's Exact test was used to compare genders. Pearson's chi-squared test was used to compare sensory block height, and the Mann-Whitney U test was used to compare the other variables. $P < 0.05$ was considered as statistically significant.

Results

Total of 76 patients (38 patients in each group) who met the inclusion criteria were included in the study. There was no difference in the demographics data respect to age, gender, weight and height between two groups (Table 1).

	Pregabalin Group (n = 38)	Control Group (n = 38)	P
Age (yr)	63.5 ± 8 (55 - 72)	66 ± 9 (57 - 75)	0.083
Gender (F/M)	35/3	33/5	0.711
Weight (kg)	81 ± 13	80 ± 14.7	0.811
Height (cm)	155 ± 7	155 ± 7.8	0.735

Table 1: *Demographic data.*
Data are mean ± standard deviation.

There was no statistical difference in the time of sensory block reached to T6 dermatome levels in two groups. The duration of two-segment regression from peak sensory block levels in pregabalin group was significantly longer than control group (70 ± 22.4 min vs. 40 ± 12.4 min, P = 0.0001). The duration of motor block was significantly longer in pregabalin group than control group (200 ± 36.7 min vs. 180 ± 26.5 min, P = 0.0001).

	Pregabalin Group (mean ± SD)	Control Group (mean ± SD)	P
Time of sensory block reached to T6 level (min)	12.5 ± 8.9	15 ± 6.2	0.233
Time of two-segment regression in sensory block (min)	70 ± 22.4	40 ± 12.4	0.0001
Duration of motor block (min)	200 ± 36.7	180 ± 26.5	0.0001

Table 2: *Parameters of sensory and motor block.*

In both groups, patients were hemodynamically stable during surgery and no patients received medications to support hemodynamics (e.g. ephedrine, phenylephrine). Serial measurements of mean arterial pressure were compared and there were no differences in two groups (Table 3).

Time (min)	Pregabalin Group (mean ± SD)	Control Group (mean ± SD)	P
0 (baseline)	105 ± 16	108 ± 16	0.627
30	85 ± 13	91 ± 14	0.458
60	88 ± 12	92 ± 12	0.669
120	89 ± 14	90 ± 16	0.565
180	88 ± 18	92 ± 15	0.233

Table 3: *Mean arterial pressure (mmHg) after spinal anesthesia.*

Discussion

In our study, time for two-segment regression of sensory block and duration of motor block in pregabalin group were significantly longer than control group. Park., *et al*. reported similar results in urogenital surgery [5]. In their study, single dose of pregabalin premedication prolonged spinal block. They measured the duration of motor block as the time of regression of spinal anesthetic from Bromage 3 (Complete motor block) to Bromage 2 (unable to flex to knees, can flex ankle). In their study, pregabalin group had significantly longer motor block (198.1 **±** 16.8 min) than control group (168.2 **±** 31.6 min). We measured the duration of motor block as the regression time from Bromage 3 (complete motor block of limb) to 0 (no motor block of limb), which measured supposedly longer period of motor block than their study. However, the duration was similar to their study (pregabalin group 200 ± 36.7 min vs. control Group, 180 ± 26.5 min). This may be attributed to the smaller dosage of bupivacaine used in our patients.

There are few studies investigated on preemptive pregabalin on postoperative analgesia [4,6]. A study by Kohli., *et al*. investigated the effect of preoperative pregabalin on postoperative analgesia in patients who underwent hysterectomy [6]. They compared 3 groups: 150 mg or 300 mg of pregabalin and the control group. Their primary outcome was the time required for first analgesic after surgery; the time was longer in both pregabalin groups than the control group. In addition, not like ours, they observed that intraoperative mean blood pressure was significantly lower in pregabalin groups compare to the control group. This difference may be also attributed to the difference in dosage of spinal anesthesia. However, the duration of spinal block was not reported in their study.

It is not clear how pregabalin prolongs duration of spinal anesthesia. Pregabalin binds to a subunit of calcium channels and reduces calcium influx to neurons. Reduced calcium influx also reduces glutamate, norepinephrine and substance P in animal models [1,7]. These effects are more significant on the sensitized spinal cord by inflammation [8,9]. Recent studies suggest that central sensitization may contribute to persistent pain in patients with osteoarthritis [10,11]. We speculate that pregabalin's antinociceptive effect is a component of prolongation of spinal anesthesia.

There are some limitations in our study. Since our study was retrospective analysis, available data were limited to certain variables. In addition, observation time was limited to intraoperative and acute postoperative period. However, we were able to address the question on the duration of spinal anesthesia.

Conclusion

Preoperative pregabalin prolongs the durations of sensory and motor blocks in patients who underwent TKA without hemodynamic changes. Further studies are warranted to investigate the mechanisms of pregabalin's effect on spinal anesthesia.

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